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Evaluation of Drug Interactions and Dosing in 484 Neurological Inpatients Using Clinical Decision Support Software and an Extended Operational Interaction Classification System (ZHIAS)

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1. Summary

Purpose: The current study aimed at identifying and quantifying critical drug interactions in neurological inpatients using Clinical Decision Support Software (CDSS). Reclassification of interactions with a focus on clinical management aimed at reducing over-alerting and enhancing the efficacy of CDSS to improve medication safety in clinical practice.

Methods: Cross-sectional study in consecutive patients admitted to the neurology ward of a tertiary care hospital. We developed a customized interface for mass analysis with the CDSS MediQ, which we used for automated retrospective identification of drug interactions during the first day of hospitalization. Interactions were reclassified according to the Zurich Interaction System (ZHIAS) that incorporates the Operational Classification of Drug Interactions (ORCA). Dose adjustments for renal impairment were also evaluated.

Results: In 484 patients with 2'812 prescriptions MediQ generated 8 "high danger", 518 "average danger" and 1'233 "low danger" interaction alerts. According to ZHIAS 6 alerts involved contraindicated and 33 provisionally contraindicated combinations, 327 a conditional, and 1'393 a minimal risk of adverse outcomes. 35 patients (6.2%) had at least one combination that was at least provisionally contraindicated. ZHIAS also provides categorical information on expected adverse outcomes and management recommendations, which are presented in detail. We identified 13 prescriptions without recommended dose adjustment for impaired renal function.

Conclusions: MediQ detected a large number of drug interactions with variable clinical relevance in neurological inpatients. ZHIAS supports the selection of those interactions that require active management, and the effects of its implementation into CDSS on medication safety should be evaluated in future prospective studies.Einleitung und Ziele

2. Introduction and goals

A number of studies have evaluated the risk of critical drug interactions and related adverse drug events (ADE) and costs in hospitalized patients.[1-5] Most studies were conducted on general medical, surgical and intensive care wards, but clinical data on medication safety in neurological

inpatients is sparse, and the clinical significance and preventability of ADE in neurology therefore remain unclear.

Clinical Decision Support Software (CDSS) can sensitively detect drug interactions and has been touted as a powerful tool to improve medication safety in clinical practice.[6 7] Furthermore CDSS may also be an efficacious tool to improve prescribing compliance with recommended doses, particularly in patients with renal impairment.[8 9] However, in spite of these convincing theoretical advantages, some recent studies concluded that over-alerting and lack of practical management recommendations often cause physicians to disregard even severe alerts.[10-13] One review concluded that between 49% and 96% of automated alerts are routinely ignored or overridden.[14] This “alert fatigue” strongly limits the acceptance of CDSS and therefore its efficacy in improving medication safety in daily practice.[15 16] Furthermore, there exists no gold standard for the classification of interactions in CDSS, and most systems use their own variation of a “traffic light system” with 3 major overall severity classes. However, it remains largely unknown how such severity grading correlates with clinical relevance, i.e. the need for active management of interactions in individual patients. The Operational Classification of Drug Interactions (ORCA) addresses this issue and particularly focuses on clinical management of interactions.[17 18] Nevertheless, there are only few studies that aimed at evaluating specific strengths and limitations of different CDSS and their classifications, and even those mostly worked with pre-selected specific drug combinations rather than clinical data.[19-21] This situation emphasizes the need for further evaluations of CDSS using real-life prescription data from representative populations and settings.

The current study therefore had the following aims: first, identification and quantification of critical drug interactions and dosing errors in a representative neurological inpatient population under natural conditions; second, reclassification of interactions by using a widely accepted system that focuses on clinical relevance of interactions and reduces over-alerting; third, further development of such a system into a classification with additional dimensions and variables that can be easily displayed in CDSS and therefore facilitate the recognition and active management of interactions in clinical practice.

3. Methods

Study population, data collection and study design

We conducted a cross-sectional study in all patients admitted to the neurology ward of the University Hospital Zurich between 1 January and 31 December 2007. There were no exclusion criteria except admissions for less than 24 hours. **Figure 1** shows an overview of the study procedures. Pharmacotherapy within the first 24 hours after admission, demographic data, medical diagnoses and laboratory test results were retrospectively retrieved for each patient from the hospital's clinical information system. After splitting medications that contained several active substances into individual components, we matched all substances to their corresponding ATC codes. Subsequently we analyzed the frequency and severity grading of drug interactions using the commercially available CDSS MediQ and then reclassified those interactions according to a new system. Furthermore, we analyzed compliance with recommended dose adjustments in patients with an estimated GFR <60 ml/min based on MediQ alerts, Aronoff's *Drug Prescribing in Renal Failure,*[22] and the manufacturers' national prescribing information.

The regional ethics committee had approved the study protocol including access to the hospital's clinical information system for study purposes.

MediQ and development of a customized interface for mass analysis of drug interactions

MediQ is a commercial CDSS for use via the Internet that features detailed comments on more than 20'000 drug interactions involving about 2'000 specific substances.[23] The user manually enters concomitantly prescribed drugs for individual patients, and MediQ subsequently identifies interactions and classifies them according to a four-level hierarchical severity grading described as: 3 = "strong" interaction with a "high danger" of resulting ADEs; 2 = "clinically relevant" interaction with an "average danger"; 1 = an interaction that is "relevant in exceptional cases" and with a "low danger"; 0 = "no interaction". MediQ also provides detailed free text information for each interaction and additional tables showing interacting pharmacokinetic and pharmacodynamic effects.

Because the manual entry of prescriptions for each patient would not be efficient for our purposes, we developed, in collaboration with the programmer of the MediQ application, a

customized data interface for mass analysis. This allowed us to upload a single structured text file over the Internet that contained the prescription information for several thousand patients at a time. Exactly the same analyses as for the usual Internet application were then executed on the MediQ server. Results could be downloaded and imported into statistical software for further analyses. MediQ's knowledge database is continuously updated, and the interaction analyses presented here were all executed in October 2010.

Zurich Interaction System (ZHIAS) classification

ZHIAS is an extended drug interaction classification system that was developed at our department during the conduct of this and other related studies. It features 4 major dimensions plus free text fields. The first dimension uses the well-documented five-level grading according to the Operational Classification of Drug Interactions (ORCA) criteria.[17 24] Briefly, ORCA's five operational levels are defined as follows: Grade 1 = "contraindicated combination"; the risk associated with the drug interaction always outweighs the benefit. Grade 2 = "provisionally contraindicated"; the combination should be avoided unless the interaction is desired or no alternative is available, monitoring may be necessary. Grade 3 = "conditional risk"; monitoring or alternatives should be considered. Grade 4 = "minimal risk"; no special action is needed. Grade 5 = "no interaction". ZHIAS' other 3 major dimensions use dichotomous variables that relate to patient management, interaction mechanisms and expected adverse effects. For the current study an expert panel consisting of one pharmacist (OZ), one senior psychiatrist (MG), two senior neurologists (AS, RG), and one senior clinical pharmacologist (SR) discussed the ZHIAS classifications of identified interactions until common agreement was achieved. For our assessments we referred to original and secondary literature, including but not limited to Hansten and Horn's *Drug Interactions: analysis and management,*[24] and *Stockley's Drug Interactions.*[25]

Data analysis

Data analysis was descriptive with presentation of results in text, tables and figures, and calculation of medians, means and proportions as appropriate. Data management and analyses were performed with STATA Version 11.1 for MacOS X (STATA corporation, College Station, TX,

USA), SPSS Version 19 for Windows (SPSS, Inc., Chicago, IL, USA), and various versions of Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

4. Results

During the study period 566 patients were admitted for at least 24 hours to the neurology ward. These patients received a total of 2'882 prescriptions involving 298 distinct substances with a median of 4 prescriptions per patient (range 0 - 21). Seventy-five patients (13.3%) had only one or no prescription and therefore did not qualify for an interaction analysis. Seven substances (nicomorphine, immunoglobulin, carnitine, alkali metal salts, clavulanic acid, tazobactam and benserazide) were excluded from further analyses because appropriate codes were missing in the MediQ database. We also excluded 2 unspecified herbal preparations and dietary supplements with unclear composition, and 4 infusion solutions, accounting for a total of 190 prescriptions. Consequently another 7 patients had only one or no prescription and were therefore not analyzed for drug interactions. Eventually, out of 2'812 individual prescriptions among the remaining subgroup of 484 patients, 2'622 (93.2%) were analyzed for interactions using MediQ.

Characteristics of all 566 patients and the subgroup of 484 patients analyzed for drug interactions are presented in **Table 1**. Overall patient characteristics were closely similar between those groups. Among the 484 patients analyzed for drug interactions the median number of concomitantly prescribed drugs per patient was 5 (range 2 - 21). Frequency of prescriptions by drug classes is shown in **Table 2**. Anticoagulants including low-dose heparins were the most commonly used drugs, prescribed to over 50% of patients.

Results of the automated drug interaction analyses using MediQ and subsequent reclassification according to ZHIAS are presented in **Tables 3-6** and **Figure 2**. Including "danger 0" comments MediQ issued an average number of 5.7 alerts per patient, with a maximum of 45 comments found in a single patient with 16 concomitant substances. The average number of interaction alerts per patient when limited to grade 1-3 was 3.6 (maximum 24 alerts per patient). Drug classes most frequently associated with clinically significant interactions according to ZHIAS were anticonvulsants (90 cases of ORCA level 1-3 interactions), followed by cardiovascular agents (77

cases), antidepressants (51 cases), anxiolytics and sedatives (50 cases), other analgesics (36 cases), and antipsychotics (35 cases). Original MediQ grading of interactions and reclassification according to ORCA criteria is shown in **Table 3**, and distribution of patients by interactions with different grading according to MediQ and after reclassification using ZHIAS in **Figure 2**. A summary of the extended ZHIAS classifications of all interactions classified as ORCA grade 1, 2 or 3 is presented in **Table 4**. Increased drug effects accounted for the majority of all interactions, the most common expected adverse events being bleeding, sedation and other CNS effects, cardiac arrhythmias and electrolyte disturbances. All specific interactions with the highest rating according to MediQ or ZHIAS, as well as the most common interactions with intermediate grading identified in our study are presented in **Tables 5 and 6**, respectively, along with their classification and expected adverse events. All combinations with the highest rating occurred only once in the study population. Of particular interest, **Table 6** shows that the combination of acetylsalicylic acid and heparins occurred in almost one third of all patients and was classified by MediQ as “average danger” with the label “clinically significant”, whereas ZHIAS classified the combination as probably desired with a mere conditional risk.

Among 554 patients with available GFR estimates 66 (11.7%) had moderate (GFR 30 - 59 ml/min), and 4 (0.7%) severe (GFR <30 ml/min) renal impairment. They had a total of 458 prescriptions for 135 distinct substances. MediQ indicated a need for dose adjustment in case of impaired renal function for 36 (26.7%) out of the 135 individual substances, accounting for 186 (40.6%) of the 458 prescriptions. Aronoff’s “Drug Prescribing in Renal Failure” recommended dose adjustments for 44 substances (32.6%), accounting for 206 prescriptions (45%). We found 13 prescriptions (6.3%) for 11 individual patients where the dose was higher than recommended and assessed the risk of a resulting ADE as major in 6, and minor in 7 patients.

5. Diskussion

The results of this study are of interest from two main points of view. First, we identified frequent and critical drug interactions that actually occurred under natural conditions in a representative neurological inpatient population. Second, in order to achieve this task we developed two

innovative methods, i.e. a customized interface for mass analysis of interactions with CDSS, and an extended drug interaction classification.

MediQ covered 291 out of 298 (97.7%) substances prescribed in the studied population, and based on its comprehensive interaction database it generated an average number of 5.7 alerts per patient. Overall, we found the comments to be informative and of good quality. On the other hand, extrapolation to a typical hospital setting where a resident may be in charge of 16 patients at a time implies that this resident would be exposed to approximately 100 alerts and comments each day issued by MediQ or any other CDSS with comparable sensitivity. Accordingly serious concerns have been expressed that such a high number of alerts typically leads to non-discriminative overriding even of severe alerts and therefore compromises the efficacy of CDSS to improve medication safety.[15 26] Furthermore, although the display of alerts can usually be filtered based on a system's severity grading, our results suggest that this is not a reliable measure to select those cases where a drug interaction requires active management. The ORCA classification has been designed with this issue in mind, and we have now extended this classification and retrospectively studied its performance in a real-life population.

Table 4 and **Figure 2** show how ZHIAS may help to focus a physician's attention on information that is relevant for clinical management of individual patients. After reclassification only 35 patients (6.2%) received alerts that indicate a "contraindicated or "provisionally contraindicated" interaction according to ZHIAS. This may be compared to 230 patients (40.6%) that fall into MediQ's top 2 severity classes of "high" and "average" danger. Such a direct comparison may be limited by the different nature of the two systems, but a look at individual combinations provides further insight into the different weighting of the two systems. Referring to the original ORCA concept we classify combinations as contraindicated when the risk always outweighs the benefit, rather than on the assumed probability and severity of the expected consequence.[17] Therefore assignments can also be primarily driven by limited evidence on a combination's benefit, which is the case for gingko biloba when combined with acetylsalicylic acid, or on an almost complete lack of efficacy, for example when oral midazolam is combined with carbamazepine.[27] Similarly, a combination of two benzodiazepines may not imply a high risk of an adverse drug event, but the

classification as „provisionally contraindicated“ according to ZHIAS points towards an unnecessary risk, unless one consciously combines different benzodiazepines based on the differences in their pharmacokinetics and therefore indications, e.g. long-acting for anxiolysis during the day and short-acting for sleep induction.

However, even such a reclassification from MediQ to ORCA does not use the full potential of the original ORCA concept to provide more specific management recommendations.[17] ZHIAS therefore features additional categorical information on management, expected adverse drug effects and thereby also on possible risk factors. The coexistence of several risk factors may even be a necessary requirement for the occurrence of an adverse drug effect in an individual patient. For example ZHIAS can readily provide the information that a patient receiving metoprolol and amiodarone should be monitored for hypotension and bradycardia, or that this combination should a priori be avoided if those signs are already preexisting. Another example that demonstrates the added value of ZHIAS is the combination of heparin plus low dose aspirin. MediQ classifies the risk as “average” and “clinically relevant”. In contrast ZHIAS considers the risk only as conditional, and the extended management classification readily indicates that this is usually a desired combination with a favorable risk-benefit ratio. Storage of this information as a categorical variable has two practical advantages. First, a ZHIAS-based CDSS could deliver such categorical information through a limited number of corresponding icons at first glance to the treating physician. This would support both, active management for prevention of adverse effects, as well as their recognition as such if they have already occurred in an individual patient. Second, the information could be linked to electronic patient data that relates to the potential adverse effects. Refined alert algorithms can then be individualized, and the resulting alerts could be more specific for each patient and thus further reduce over-alerting. For example hyponatremia or QTc prolongation could be displayed with a high level of importance if they are recognized as a potential adverse effect of a prescribed combination *and* if the CDSS automatically receives the information that they are indeed present in an individual patient.

Another intriguing perspective that arises from our study is the possibility to conduct highly efficient mass analyses, which require solutions such as our customized interface between

electronic prescription data and CDSS. Retrospective analyses can then guide the development of prospective preventive strategies that target those drug interactions that were identified to occur with a certain frequency and actually lead to adverse drug effects in a given setting. Our results support the view that a limited number of critical combinations account for a large part of all critical interactions in practice. Consequently, during our regular neurology ward rounds we are now able to address particularly those drug interactions that the current study identified to be frequent and clinically relevant in this setting. Whether such an approach will indeed be able to reduce ADE must be further investigated, but previous studies have shown that the selection of specific targets and application of targeted electronic interventions on pharmacotherapy can indeed be an efficacious and efficient method in order to improve clinical outcomes.[28]

Our study is also subject to some important limitations. First, it was not designed to search for interactions beyond those identified by MediQ, although we plan to address this point in future studies that compare several different CDSS. Neither did we determine the frequency of ADE associated with drug interactions, which would have been difficult in retrospective and also be underpowered given the limited number of studied patients. Furthermore, the absence of a gold standard is a challenge for all attempts to classify drug interactions. Poor accordance between different systems has been demonstrated,[29-31] and even within the same system there is interrater variability.[18 32] This also applies to ORCA, where our personal assessment as part of ZHIAS sometimes deviated from Hansten & Horn's own ORCA class. However, we tried to minimize the subjective component by setting up an expert panel where we also used widely recognized and regularly updated reference texts as a basis for our judgments. Finally, we had to limit our study period to the end of 2007 because thereafter the regular presence of clinical pharmacologists at ward rounds would have affected the "natural" frequency of interacting prescriptions.

In conclusion, our study was able to identify drug interactions in neurological inpatients with a new and highly efficient solution for CDSS-based automated mass analysis. Subsequent reclassification of interactions according to a new extended classification allowed us to select a smaller number of contraindicated combinations and interactions that likely require active clinical management, and to describe expected adverse effects that can also point towards associated

risk factors. The implementation of ZHIAS in CDSS may reduce over-alerting and improve usability and efficacy of CDSS to prevent ADE in clinical practice, which should be evaluated in future prospective studies.

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7. Tables

Table 1 - Characteristics of the study population

Characteristics	All patients		Patients analyzed for drug interactions[1]	
	n	%	n	%
Total	**566**	**100**	**484**	**100**
Sex				
Female	314	55.5	264	54.5
Male	252	44.5	220	45.5
Age category (years)				
<25	22	3.9	19	3.9
25-44	125	22.1	96	19.8
45-64	205	36.2	172	35.5
65-84	200	35.3	184	38.0
85 and older	14	2.5	13	2.7
Primary admission diagnosis [2]				
Cerebrovascular events	227	40.1	206	42.6
Inflammatory and demyelinating diseases	78	13.8	67	13.8
Epilepsy / seizures	55	9.7	45	9.3
Headache, migraine and other pain syndromes	46	8.1	39	8.1
Cognition, perception, speech and visual disturbance	45	8.0	34	7.0
Parkinson's disease / movement disorders	36	6.4	29	6.0
Malignant or benign brain neoplasms	28	4.9	25	5.2
Paralytic syndromes	26	4.6	19	3.9
Other	25	4.4	20	4.1
At least one secondary psychiatric diagnosis	102	18.0	84	17.4
Renal function (MDRD-GFR)				
≥60 mL/min	484	85.5	412	85.1
30-60 mL/min	66	11.7	63	13.0
<30 mL/min	4	0.7	4	0.8
No information available	12	2.1	5	1.0

[1] Drug interactions were not analyzed in 75 patients that received only one or no drug, and in another 7 patients that received only one or no drug that was contained in the MediQ database.
[2] Only one primary diagnosis per patient

Table 2 - Pharmacotherapy within 24 hours after admission in 484 patients analyzed for drug interactions by MediQ

Drugs	**n prescriptions**		**n patients with prescriptions**	
	n	**%**	**n**	**%**
Total	**2'812[1]**	**100**	**484**	**100**
Anticoagulants (including low-dose heparins)	316	11.2	270	55.8
Vitamins and mineral supplements	267	9.5	74	15.3
Acetylsalicylic acid (low dose)	197	7.0	197	40.7
Analgesics and antipyretics	186	6.6	145	30.0
Renin-angiotensin-aldosterone system inhibitors and diuretics	183	6.5	120	24.8
Antipsychotics, anxiolytics, sedatives and hypnotics	181	6.4	144	29.8
Anticonvulsants	177	6.3	115	23.8
Lipid-lowering agents	163	5.8	157	32.4
Other blood modifiers/volume expanders	143	5.1	133	27.5
Other cardiovascular agents	133	4.7	107	22.1
Proton pump inhibitors	124	4.4	124	25.6
Hormones	116	4.1	109	22.5
Antidepressants	98	3.5	86	17.8
Anti-infective agents	83	3.0	53	11.0
Other nervous system agents	76	2.7	65	13.4
Other gastrointestinal agents	70	2.5	52	10.7
Anti-Parkinson agents	62	2.2	24	5.0
Antidiabetic agents	56	2.0	38	7.9
Ophthalmic and respiratory tract agents	51	1.8	30	6.2
Special nutrition and herbal medicines	48	1.7	46	9.5
Antineoplastic and immunological agents	31	1.1	28	5.8
Other	51	1.8	46	9.5

[1]Out of 2'812 individual prescriptions, only 2'622 (93.2%) were later analyzed for interactions by MediQ because 13 substances accounting for 190 prescriptions were not contained in its database (see results for details).

Table 3 - Identification and grading of interactions by MediQ and subsequent reclassification based on ORCA criteria as part of the ZHIAS classification

Drug interaction classifications	**Frequency of distinct combinations in 484 patients**		**Frequency of interaction alerts in 484 patients**	
	n	**%**	**n**	**%**
MediQ level 3 ("high danger")	**8**	**100.0**	**8**	**100.0**
ORCA level 1 ("contraindicated")	2	25.0	2	25.0
ORCA level 2 ("provisionally contraindicated")	1	12.5	1	12.5
ORCA level 3 ("conditional risk")	5	62.5	5	62.5
ORCA level 4 ("minimal risk")	0	0.0	0	0.0
MediQ level 2 ("average danger")	**164**	**100.0**	**518**	**100.0**
ORCA level 1 ("contraindicated")	3	1.8	3	0.6
ORCA level 2 ("provisionally contraindicated")	19	11.6	29	5.6
ORCA level 3 ("conditional risk")	85	51.8	272	52.5
ORCA level 4 ("minimal risk")	57	34.8	214	41.3
MediQ level 1 ("low danger")	**486**	**100.0**	**1'233**	**100.0**
ORCA level 1 ("contraindicated")	1	0.2	1	0.1
ORCA level 2 ("provisionally contraindicated")	3	0.6	3	0.2
ORCA level 3 ("conditional risk")	37	7.6	50	4.1
ORCA level 4 ("minimal risk")	445	91.6	1179	95.6
MediQ level 0 ("no interaction")	**454**	**100.0**	**1'004**	**100.0**

Table 4 - Summary of full ZHIAS classification stratified over ORCA classes 1 to 3 for all interactions identified by MediQ with corresponding frequencies in 484 analyzed patients

ZHIAS classification	**Frequencies in 484 patients, stratified over ORCA classes**		
	ORCA 1 (contraindicated)	**ORCA 2 (provisionally contraindicated)**	**ORCA 3 (conditional risk)**
	n (%)	**n (%)**	**n (%)**
TOTAL combinations	6 (100.0)	33 (100.0)	327 (100.0)
Management			
Desired	0 (0.0)	22 (66.7)	191 (58.4)
Consider alternative	6 (100.0)	12 (36.4)	131 (40.1)
Monitoring	0 (0.0)	33 (100.0)	323 (98.8)
Mechanism[1]			
Pharmacokinetic	4 (66.7)	14 (42.4)	103 (31.5)
Pharnacodynamic	2 (33.3)	31 (93.9)	276 (84.4)
Expected adverse effects			
Increased drug effect	2 (33.3)	26 (78.8)	210 (64.2)
Decreased drug effect	4 (66.7)	4 (12.1)	53 (16.2)
Sedation (CNS)	0 (0.0)	20 (60.6)	24 (7.3)
Serotonin syndrome	0 (0.0)	2 (6.1)	17 (5.2)
Extrapyramidal symptoms	0 (0.0)	4 (12.1)	3 (0.9)
Seizures	0 (0.0)	4 (12.1)	17 (5.2)
CNS effects other	0 (0.0)	3 (9.1)	32 (9.8)
Nephrotoxicity	0 (0.0)	0 (0.0)	6 (1.8)
Hepatotoxicity	0 (0.0)	0 (0.0)	13 (4.0)
QTc prolongation	0 (0.0)	2 (6.1)	22 (6.7)
Cardiac arrhythmias	0 (0.0)	6 (18.2)	33 (10.1)
Thrombosis	0 (0.0)	0 (0.0)	5 (1.5)
Bleeding	2 (33.3)	1 (3.0)	149 (45.6)
Blood pressure up	0 (0.0)	1 (3.0)	6 (1.8)
Blood pressure down	0 (0.0)	5 (15.2)	17 (5.2)
Cardiovascular effects other	0 (0.0)	1 (3.0)	7 (2.1)
Hyperkalemia	0 (0.0)	0 (0.0)	11 (3.4)
Hypokalemia	0 (0.0)	0 (0.0)	6 (1.8)
Hyponatremia	0 (0.0)	0 (0.0)	13 (4.0)
Metabolic/endocrine effects	1 (16.7)	2 (6.1)	6 (1.8)
Gastrointestinal toxicity	0 (0.0)	1 (3.0)	14 (4.3)
Muscular toxicity	0 (0.0)	0 (0.0)	6 (1.8)
Hematotoxicity	0 (0.0)	2 (6.1)	2 (0.6)
Allergy/skin reactions	0 (0.0)	0 (0.0)	15 (4.6)
Other	0 (0.0)	0 (0.0)	3 (0.9)

[1] Categories are not mutually exclusive and can therefore exceed 100%.

Table 5 - Presentation of all specific interactions with the highest rating according to MediQ or ZHIAS, i.e. for MediQ grade 3, "high danger", or for ZHIAS ORCA grade 1, "contraindicated"[1]

		ZHIAS classification		
Drug combination[2]	**MediQ danger**	**ORCA**	**Management[3]**	**Expected adverse effects**
Atazanavir - omeprazole	High	1	A	Loss of atazanavir efficacy
Midazolam p.o. - carbamazepine	High	1	A	Loss of midazolam efficacy
Haloperidol - sulpiride	High	2	D / M	EPS, QTc prolongation
Acetylsalicylic acid low dose – methotrexate low dose	High	3	A / M	Bone marrow toxicity
Fluoxetine - tramadol	High	3	A / M	Serotonin syndrome, seizures
Paroxetine - venlafaxine	High	3	D / M	Serotonin syndrome, QTc
Phenytoin - valproate	High	3	D / M	Sedation, hepatotoxicity
Lisinopril - spironolactone	High	3	A / M	Hyperkalemia
Gingko biloba - dalteparin	Average	1	A	Bleeding
Midazolam - St. John's wort	Average	1	A	Loss of efficacy
Olanzapine - carbamazepine	Average	1	A	Loss of efficacy, metabolic
Ginkgo biloba - acetylsalicylic acid	Low	1	A	Bleeding

[1] Each listed combination occurred only once in the studied population

[2] ORCA notation: 1 = contraindicated, 2 = provisionally contraindicated, 3 = conditional risk. Assignment to ORCA class 1 "contraindicated" does not necessarily imply a high risk of an ADE. It means that the risk also outweighs the benefit, i.e. the assignment can primarily be driven by limited evidence on a drug's benefit, such as for gingko biloba.

[3] A = consider an available alternative; D = desired interaction; M = special monitoring recommended

Table 6 - Presentation of the 5 most frequent specific drug interactions classified by ZHIAS as ORCA 2 ("provisionally contraindicated"), and the 10 most frequent combinations classified by ZHIAS as ORCA 3 ("conditional risk") in 484 analyzed patients.

				ZHIAS classification		
Combination name	**Frequency in 484 patients**		**MediQ danger**	**ORCA[1]**	**Management[2]**	**Expected adverse effects**
	n	**%**				
5 most frequent combinations classified as "provisionally contraindicated" by ZHIAS						
Any combination of two benzodiazepines	12	2.5	Average or low	2	D / M	Sedation
Metoprolol - amiodarone	4	0.8	Average	2	A / M	Hypotension, bradycardia
Zolpidem and any benzodiazepine	4	0.8	Average or low	2	D / M	Sedation
Carbamazepine - metoclopramide	2	0.4	Average	2	A / M	Seizures, other CNS effects
Carbamazepine - tramadol	2	0.4	Average	2	A / M	Sedation, seizures, loss of analgesia
10 most frequent combinations classified as "conditional risk" by ZHIAS						
Acetylsalicylic acid (low dose) - heparins	140	28.9	Average	3	D / M	Bleeding
Acetylsalicylic acid - corticosteroids	11	2.3	Average	3	A / M	GI ulceration
Lamotrigine - valproate	9	1.9	Average	3	D / M	Other CNS effects, skin reactions
Carbamazepine - paracetamol	7	1.4	Average	3	A / M	Hepatotoxicity
Levothyroxine – calcium or magnesium hydroxide	7	1.4	Average or low	3	M	Loss of thyroid hormone efficacy
Tramadol - tricyclic antidepressants	5	1.0	Average	3	A / M	Serotonin syndrome, seizures
Amlodipine - metoprolol	4	0.8	Average	3	D / M	Hypotension, bradycardia
Atorvastatin- amiodarone	4	0.8	Average	3	A / M	Muscle toxicity
Clonazepam - valproate	4	0.8	Low	3	D / M	Absence seizures, sedation
Carbamazepine - lamotrigine	3	0.6	Average	3	D / M	Other CNS effects, skin reactions
Citalopram - hydrochlorothiazide	3	0.6	Low	3	A / M	Hyponatremia

[1] ORCA notation: 1 = contraindicated, 2 = provisionally contraindicated, 3 = conditional risk.
[2] Management notation: A = consider an available alternative; D = desired interaction; M = special monitoring recommended

8. Figures

Figure 1: Overview of the study procedur

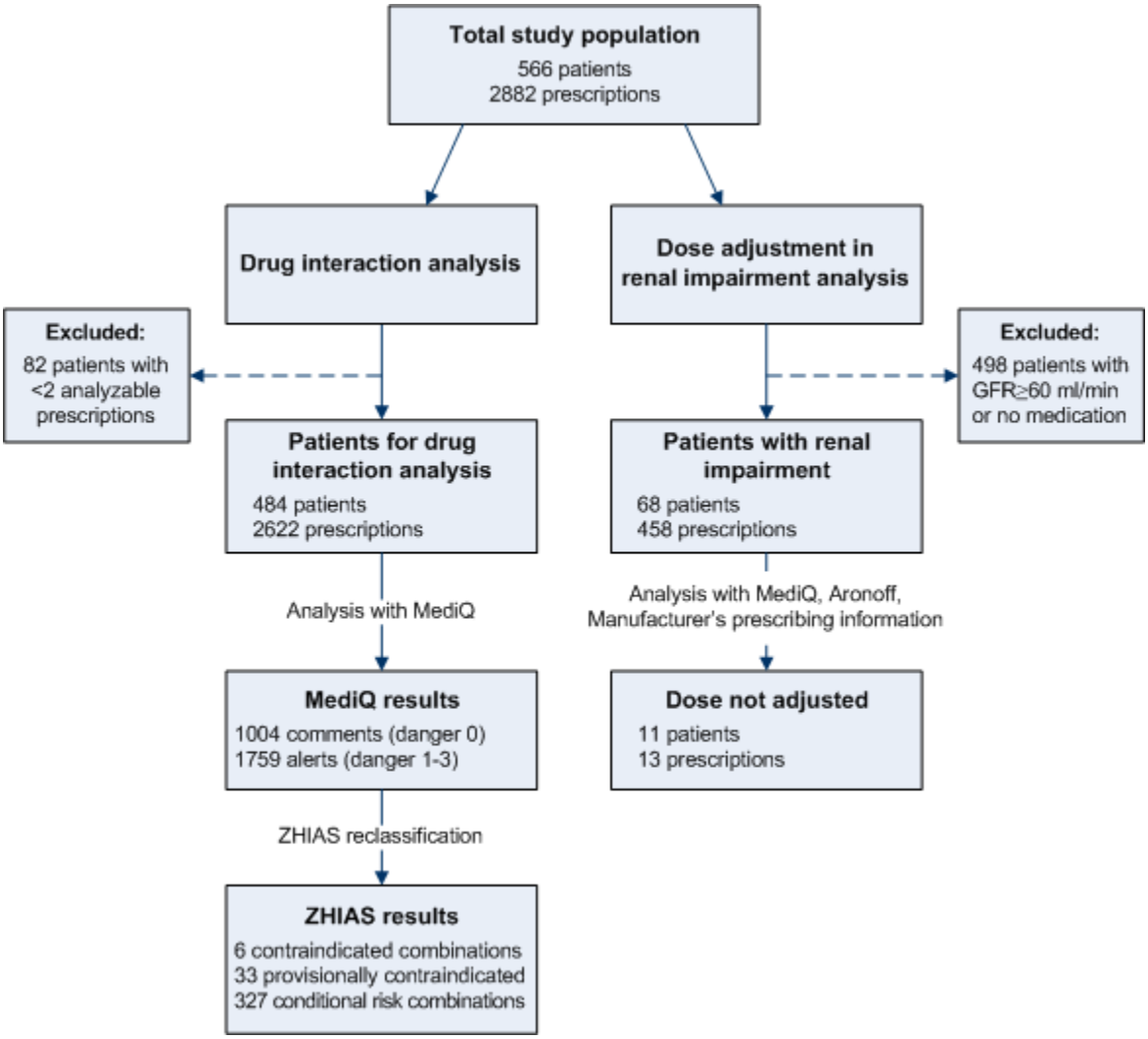

Figure 2: Interaction grading according to MediQ and after ZHIAS reclassification

The presented distributions are based on individual patients where each patient is counted only once and assigned according to the interaction with the highest grade found in that patient.

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10. Curriculum Vitae

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bis	03/2010	100% -Ambulatorium Aarau
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